Communication from the ASGE Technology Committee

REPORT ON EMERGING TECHNOLOGY

Endoscopic anti-reflux devices (with videos)

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This document was reviewed and approved by the governing board of the American Society for Gastrointestinal Endoscopy.

The American Society for Gastrointestinal Endoscopy (ASGE) Technology Committee provides reviews of existing, new, or emerging endoscopic technologies that have the potential to affect the practice of GI endoscopy. Evidence-based methodology is used, with a MEDLINE literature search to identify pertinent preclinical and clinical studies on the topic and a MAUDE (Food and Drug Administration Center for Devices and Radiological Health) database search to identify the reported adverse events of a given technology. Both are supplemented by accessing the "related articles" feature of PubMed and by scrutinizing pertinent references cited by the identified studies. Controlled clinical trials are emphasized, but in many cases, data from randomized controlled trials are lacking. In such cases, large case series, preliminary clinical studies, and expert opinions are used. Technical data are gathered from traditional and Web-based publications, proprietary publications, and informal communications with pertinent vendors. For this review, the MEDLINE database was searched through December 2015 by using the keywords "gastroesophageal reflux disease," "GERD," "endoscopic surgery," "minimally invasive treatment," "endoscopic treatment," "radiofrequency," "radiofrequency energy," "Stretta," "endoscopic fundoplication," "endoscopic incisionless fundoplication," and "fundoplication." Reports on Emerging Technologies are drafted by 1 or 2 members of the ASGE Technology Committee, reviewed and edited by the committee as a whole, and approved by the governing board of the ASGE. These reports are scientific reviews provided solely for educational and informational purposes. These reports on emerging technologies are not rules and should not be construed as establishing a legal standard of care or as encouraging, advocating, requiring, or discouraging any particular treatment or payment for such treatment.

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0016-5107/$36.00
http://dx.doi.org/10.1016/j.gie.2017.08.001

BACKGROUND

GERD is one of the most common GI diseases, accounting for 7 million annual outpatient visits in the United States.[1] Lifestyle modification and medical therapy, including acid-suppressive medications, are first-line treatments for GERD.[2,3] In approximately 30% to 40% of patients with GERD, medical therapy provides only partial relief of symptoms.[4] Laparoscopic anti-reflux surgery remains an option for patients with GERD, but only approximately 1% of all patients with GERD opt for surgical intervention.[5] To address this GERD treatment gap, minimally invasive endoscopic anti-reflux devices have been developed, which allow endoscopic fundoplication or reduction in lower esophageal sphincter (LES) compliance.

Endoscopic anti-reflux devices are intended to target patients with GERD with mild gastroesophageal junction (GEJ) defects. These devices do not alter the anatomy of the esophagus, GEJ, or stomach and, thus, should not be considered as alternatives to surgical fundoplication for patients with significant anatomic abnormalities including large hiatal or paraesophageal hernias. Use of these devices has not been systematically evaluated in patients with active erosive esophagitis, Barrett's esophagus, esophageal motility disorders, or hiatal hernias >2 cm in length. Limited data exist regarding use of these devices to treat patients with nonerosive reflux disease and laryngopharyngeal reflux disease. This document focuses on endoscopic anti-reflux devices to treat patients with GERD.

Although many endoscopic anti-reflux devices have undergone testing in bench models, animal models, and

human trials, only a few are available currently in the United States for clinical use. The currently available U.S. Food and Drug Administration (FDA) approved devices for the endoscopic treatment of GERD are: transoral incisionless fundoplication (TIF) (EsophyX device; EndoGastric Solutions, Redmond, Wash, USA), Medigus Ultrasonic Surgical Endostapler (MUSE) (Medigus Ltd, Omer, Israel), and Stretta (Mederi Therapeutics, Greenwich, Conn, USA). Several previously developed endoscopic antireflux devices including the EndoCinch device (CR Bard, Inc, Murray Hill, NJ, USA), Endoscopic Suture device (Wilson-Cook, Winston-Salem, NC, USA), Endoscopic Plication System (Plicator; NDO Surgical, Inc, Mansfield, Mass, USA), Enteryx (Boston Scientific Corp, Boston, Mass, USA), and Gatekeeper reflux repair system (Medtronic Inc, Minneapolis, Minn, USA) are no longer marketed because of safety concerns and lack of efficacy.

TECHNOLOGY UNDER REVIEW

EsophyX device

TIF, with the use of the EsophyX device, was introduced as an endoscopic substitute for surgical reconstruction of the LES. The procedure aims to restore the angle of His (the acute angle between the cardia and the esophagus). The TIF procedure has evolved over time from a gastrogastric plication to an esophagogastric plication. In the initially described TIF procedure (TIF 1.0), fasteners were placed 1 cm above the GEJ, and no circumferential wrap was created. In the TIF 2.0 procedure, fasteners are placed 1 to 3 cm above the GEJ, and additionally, a circumferential wrap is created. The TIF 2.0 procedure improves the antireflux barrier by reducing small hiatal hernias ($\leq$2 cm), if present, and by creating a valve 2 to 4 cm in length with a >270° circumferential fundoplication. The FDA cleared the EsophyX device in September 2007. TIF requires general anesthesia and is routinely performed in the operating room, with patients requiring postprocedure hospitalization for observation.

Description of device. The EsophyX device is a single-use device and consists of multiple parts, including a tissue mold and chassis, a helical retractor, an invaginator, and a stylet-fastener assembly (Fig. 1A and B). The tissue mold can be flexed and extended to approximate and compress together esophageal and gastric fundal tissue during the procedure. The tissue mold and chassis are rotated around the GEJ during the procedure to create a circumferential wrap. The helical retractor is used to anchor and pull down the GEJ tissue into the tissue mold during fundoplication. The invaginator is connected to wall suction and allows anchoring of the esophagus to the chassis of the EsophyX device and facilitates reduction of small hiatal hernias (by means of advancing the EsophyX device caudally into the stomach) and placement of fasteners (by anchoring the distal esophagus to the device). The EsophyX device uses SerosaFuse fasteners (EndoGastric Solutions, Redmond, Wash, USA) to plicate esophageal and gastric tissue. SerosaFuse fasteners are nonbiodegradable, H-shaped, polypropylene fasteners, available in 6.5 mm and 7.5 mm lengths (Video 1, available online at www.giejournal.org).

The original EsophyX device and the subsequent $EsophyX_2$ device have been replaced by 2 newer versions of the $EsophyX_2$ device. The $EsophyX_2$ HD is compatible with gastroscopes with outer diameters ranging from 10.6 mm to 12.3 mm and with both lengths of SerosaFuse fasteners. The EsophyX Z device is compatible with gastroscopes with outer diameters ranging from 4.7 mm to 7.2 mm, is compatible only with 7.5 mm–length fasteners, and includes a fastener delivery trigger (Fig. 2A and B).

Description of technique. Two endoscopists are necessary for this procedure; the first operates a gastroscope to provide visual guidance to the second who uses the EsophyX device to achieve the fundoplication. The EsophyX device is loaded over the shaft of a compatible gastroscope. The gastroscope and the EsophyX device (with its tissue mold extended) are advanced to the stomach under direct vision. Once in the stomach, the gastroscope is retracted back into the chassis, and the tissue mold is flexed, exposing a dedicated opening between the chassis and tissue mold, through which the gastroscope can be advanced. The gastroscope is then retroflexed to provide an endoscopic view of the gastric cardia, while the second endoscopist uses the EsophyX device to create a fundoplication.

The helical retractor is inserted into the tissue of the GEJ by means of corkscrew-like rotation and is then used to pull the tissue down and/or caudally. This leads to folding of the cardiac notch of the stomach, with approximation of the serosal surfaces of the gastric fundus and lower esophagus. The tissue mold and the invaginator buttress this approximation from the gastric and esophageal sides, respectively. Finally, the stylet-fastener assembly places 2 SerosaFuse fasteners through this newly formed fold (Fig. 3). The EsophyX device is then rotated on its long axis, and the process is repeated 9 to 10 times until approximation is achieved around 270° (200°-300°) of the GEJ. Approximately 20 fasteners are implanted during the procedure to create fusion of the esophageal and gastric fundal tissue (Fig. 3).

MUSE

MUSE is an endoscopic stapling system that creates a partial fundoplication. Although the surgical and anatomic principles behind MUSE are similar to that of TIF, the apparatus used differs significantly. The FDA cleared the MUSE system in January 2015. The MUSE procedure requires general anesthesia and is typically performed in the operating room, with patients requiring postprocedure hospitalization for observation.

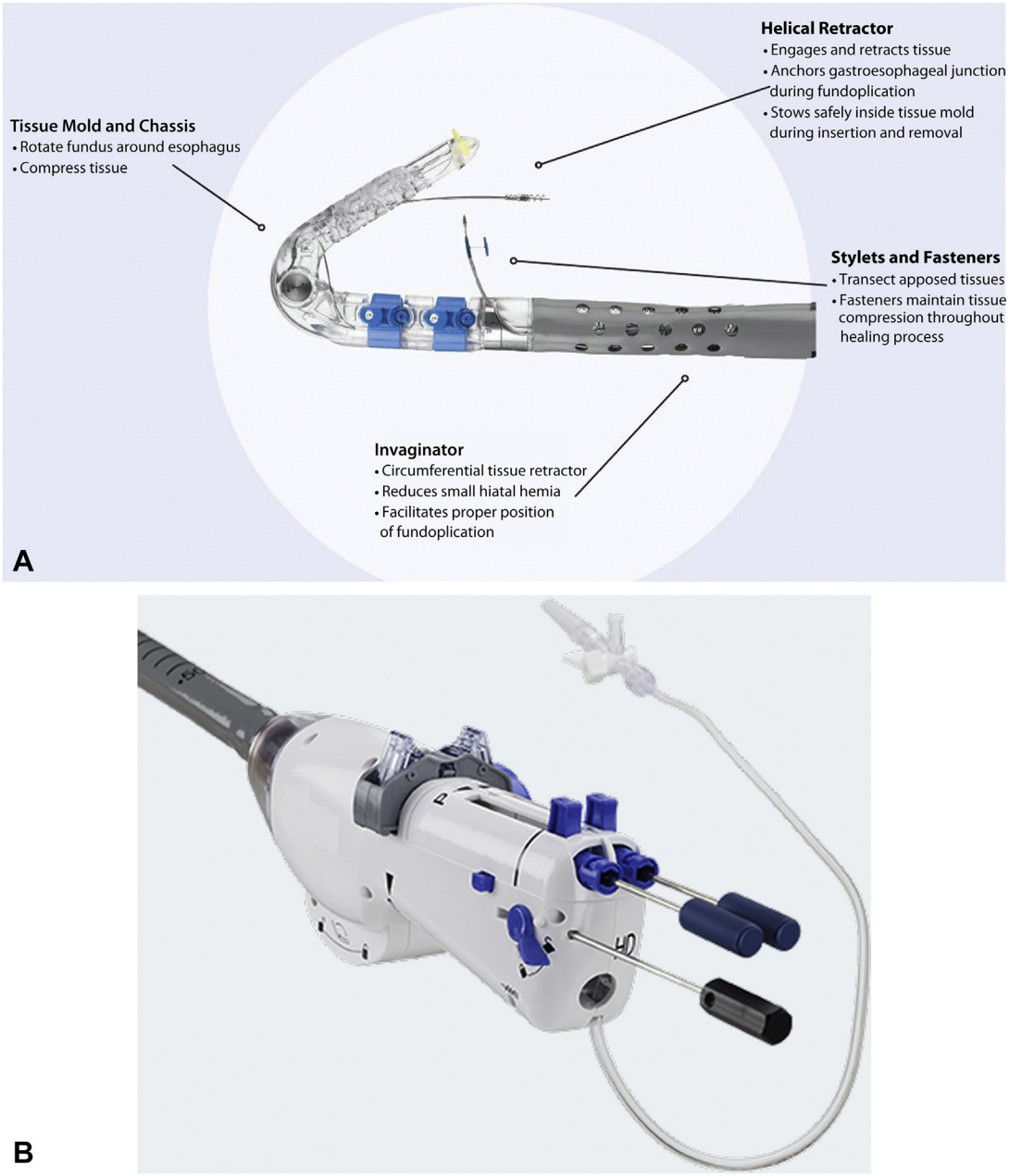

Figure 1. EsophyX$_2$ HD device. **(A)** Tip and **(B)** control body (EndoGastric Solutions, Redmond, Wash).

Description of device. MUSE is made up of a single-use flexible endostapler, a light source, and a control unit, the MUSE console (Fig. 4A). The endostapler resembles an endoscope and has a handle with tip deflection controls, an 80 cm–long shaft, and a 66 mm–long rigid section in the midportion of the endoscope shaft. The rigid section contains an ultrasonic mirror, a surgical stapler oriented perpendicular to the endoscope, a cartridge carrying five 4.8-mm standard B-shaped titanium surgical staples, and 2 nuts. The endoscope shaft has channels for suctioning, air insufflation, and irrigation. The tip of the endoscope has a video camera, a light source, an anvil to bend the staples, an ultrasonic range finder, and 2 reference screws that are secured by the 2 nuts in the cartridge at the endoscope mid-shaft during use (Fig. 4B).

Description of technique (Video 2, available online at www.giejournal.org). After the surgical staples in the staple cartridge within the rigid section on the endoscope shaft are manually loaded, the MUSE device is introduced into the esophagus through a previously placed overtube (17-mm internal diameter, 19.5-mm outer diameter). During the procedure, the endoscope is retroflexed in the stomach. After a stapling location is

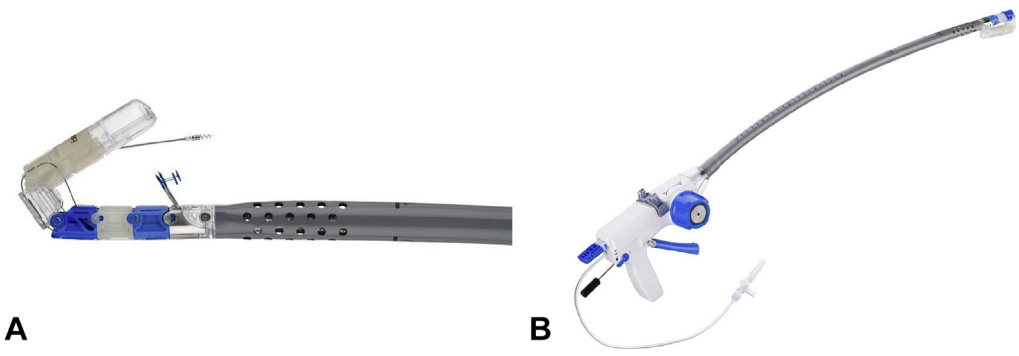

Figure 2. EsophyX$_2$ Z device. **(A)** Tip and **(B)** instrument (EndoGastric Solutions, Redmond, Wash).

identified, the section of the endoscope shaft with the staple cartridge is gently pulled back into the esophagus, so that the staple cartridge is positioned approximately 3 cm proximal to the GEJ. The tip of the endoscope is then retroflexed and bent to allow the anvil to engage with the rigid section of the endoscope shaft housing the staple cartridge, thereby clamping tissue of the fundus against the distal esophagus. The ultrasonic range finder checks the tissue gap and alignment between the staple cartridge (at the endoscope mid-shaft) and anvil (at the endoscope tip) and displays this data on a video monitor on the control unit. The reference screws at the endoscope tip are then deployed and are engaged and secured by the 2 nuts in the staple cartridge. This allows the alignment and tissue compression to be held until the staples are fired. Once the endoscopist is satisfied with the positioning of the device and tissue thickness (1.4-1.6 mm), the staples are fired. The screws are then disengaged, and the MUSE device is rotated, and the entire process is repeated twice until a 180° anterior fundoplication is achieved (Fig. 5).

Stretta

Stretta acts via the administration of radiofrequency (RF) energy to the muscle layer of the LES. Although the exact mechanism of action has not been determined, Stretta reduces the number of transient lower esophageal sphincter relaxations and decreases LES compliance.[6] The FDA originally cleared Stretta in 2000. The RF generator received an updated clearance in 2011. Stretta can be performed in a routine outpatient setting with patients under moderate sedation or monitored anesthesia care with propofol.

Description of device. The Stretta apparatus is made up of a 4-channel RF generator and a catheter. The monopolar RF generator has ports to allow attachment of a grounding pad, the Stretta catheter, an irrigation pump, and a foot-pedal control switch. The RF generator has 4 operational modes, including stand-by, ready, RF-on, and RF-delay.

The Stretta catheter has a handle at 1 end and a noncompliant balloon with an overlying 4-needle assembly at its distal end (Fig. 6). The handle has ports for balloon inflation and for connecting suction and irrigation. A connecting cable attached to the handle of the Stretta catheter allows the generator to deliver RF energy to the needle assembly. The balloon is inflated with a maximum of 25 mL of air. A 60-mL syringe with a pressure release valve is used to inflate and deflate the balloon during the procedure, with overinflation automatically prevented by the pressure release valve. The needle assembly consists of 4 curved needles that incorporate a thermocouple at the tip and base of the needle to regulate temperatures at the muscularis propria and mucosa, respectively.

Stretta delivers low-power RF energy to the muscularis propria of the lower esophagus. The RF generator, by means of 4 independently controlled channels, delivers up to 5 W per channel at 460 kHz frequency to the needle electrodes. Proper placement of the needle electrodes within the muscularis propria is confirmed by impedance measurements. If the impedance measurements are out of an acceptable range (50-1000 Ω), treatment does not progress. The desired target temperature at the muscle layer is 65° to 85°C. The surface mucosal temperature is maintained below 50°C by continuous irrigation with cold water delivered to the catheter via a peristaltic pump that automatically increases the irrigation flow rate when the mucosal temperature rises. A dynamic feedback power-control loop with real-time continuous temperature monitoring allows the RF generator to automatically control power in each independent channel to prevent overheating and ablation of tissue. Power delivery ceases automatically if the muscle layer temperature exceeds 85°C, surface mucosal layer temperature exceeds 50°C, or impedance exceeds 1000 Ω.

Description of technique (Video 3, available online at www.giejournal.org). An upper endoscopy is performed to measure the distance between the GEJ and the bite block. A guidewire is then advanced into the stomach, and the endoscope is removed. Subsequently, the Stretta catheter is advanced over the guidewire, and

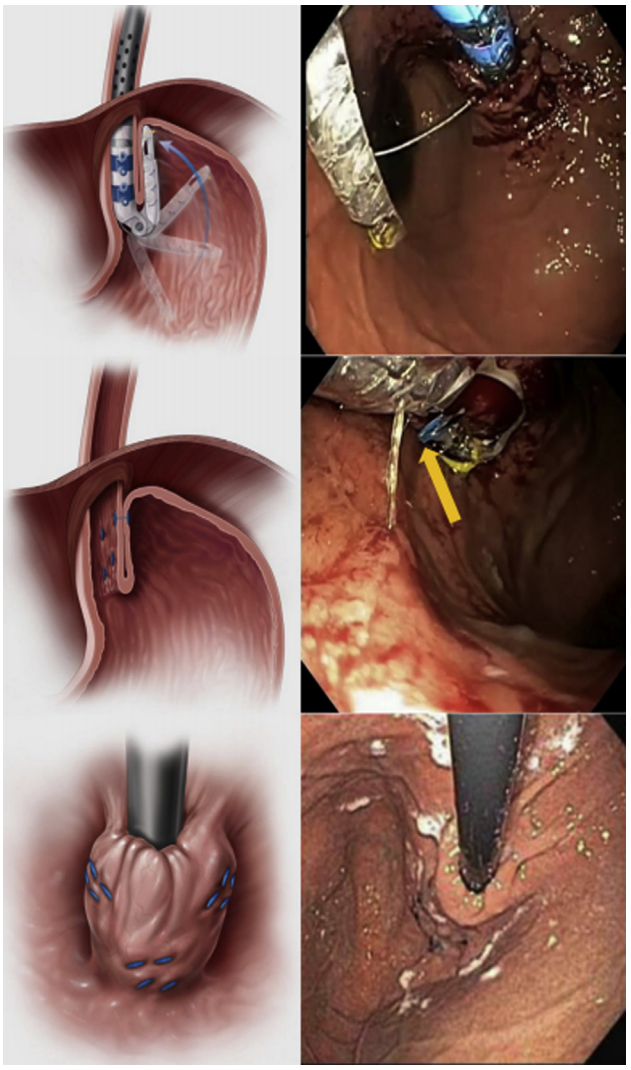

Figure 3. TIF (transoral incisionless fundoplication) 2.0 procedure (EsophyX device; EndoGastric Solutions, Redmond, Wash). Reprinted with permission. Hunter et al.[7]

the procedure is performed without endoscopic visualization. For antegrade treatment application, the Stretta catheter is advanced over the guidewire to 1 cm proximal to the Z line, with its balloon deflated and needles retracted. The balloon is then inflated by insufflation with 25 cc of air to approximate the needle assembly to the mucosa. RF energy is applied at a total of 6 treatment levels, including 4 antegrade treatment levels and 2 retrograde levels in the proximal stomach by the pull-back technique (Fig. 7). The upwardly curved needle electrodes are then deployed outward to a length of 5.5 mm, and RF energy delivery is then initiated. The upwardly curved design of the needle reduces the risk of inadvertent transmural penetration and administration of RF energy to the mediastinal space.

After completion of the first cycle of RF energy delivery, the needles are retracted, and the balloon is deflated. The Stretta catheter is then pulled back 2 cm, rotated 45°, and advanced back to the same level (1 cm above the Z line) where this process is repeated, thus creating 8 treatment sites at the first level. After completion of the first treatment level, the catheter is then advanced incrementally by 5 mm to 3 additional levels, up to 5 mm below the Z line, to allow application of RF energy at a total of 32 sites at 4 levels straddling the Z line.

After completion of antegrade treatment, RF energy is then delivered at the proximal stomach by inflating the balloon sequentially with 25 cc and then with 22 cc of air and slowly retracting the balloon catheter to approximate the needle assembly with the mucosa of the gastric cardia at 2 levels. At each treatment level in the proximal stomach, RF energy is applied at 12 sites by rotation of the catheter 30° to the left and then 30° to the right, from the initial treatment position. In total, RF energy is applied at 56 sites at 6 levels (32 antegrade treatment sites and 24 retrograde treatment sites) (Fig. 7).

CLINICAL RESULTS

TIF

Randomized clinical trials. Four randomized clinical trials have evaluated the TIF 2.0 procedure with the use of the EsophyX$_2$ device in the treatment of GERD (Table 1). The RESPECT (randomized EsophyX vs sham, placebo-controlled transoral fundoplication) study, a multicenter, blinded, randomized controlled trial, compared the TIF 2.0 procedure plus placebo medication with a sham procedure plus optimized proton pump inhibitor (PPI) therapy in patients with a history of troublesome regurgitation and GERD symptoms for >6 months despite PPI therapy.[7] The primary endpoint of this study was the elimination of troublesome regurgitation, as defined per the Montreal consensus[8] at the end of 6 months of follow-up. In the TIF/placebo group, 67% (58 of 87) of patients reported elimination of regurgitation compared with 45% (19 of 42) of patients in the sham/PPI group ($P = .023$).[7] Analysis of objective parameters of acid exposure revealed that the TIF/placebo treatment group had superior outcomes compared with the sham/PPI group with regard to the number of reflux episodes, percentage of time esophageal pH was <4, and the DeMeester score.[9] At the end of 6 months, the TIF/placebo group showed a reduction in the average number of reflux episodes from 135 to 94 ($P < .001$), the percentage of time the esophageal pH was <4 decreased from 9.3% to 6.4% ($P < .001$), and the average DeMeester score decreased from 33.6 to 23.9 ($P < .001$).[9] In the sham/PPI group, it was observed that there was no significant improvement in any objective parameter. Over a follow-up of up to 18 months, 72% (63 of 87) of the TIF group patients were completely off PPI therapy, whereas 71% (30 of 42) of sham/PPI patients elected to cross over and receive a TIF procedure.

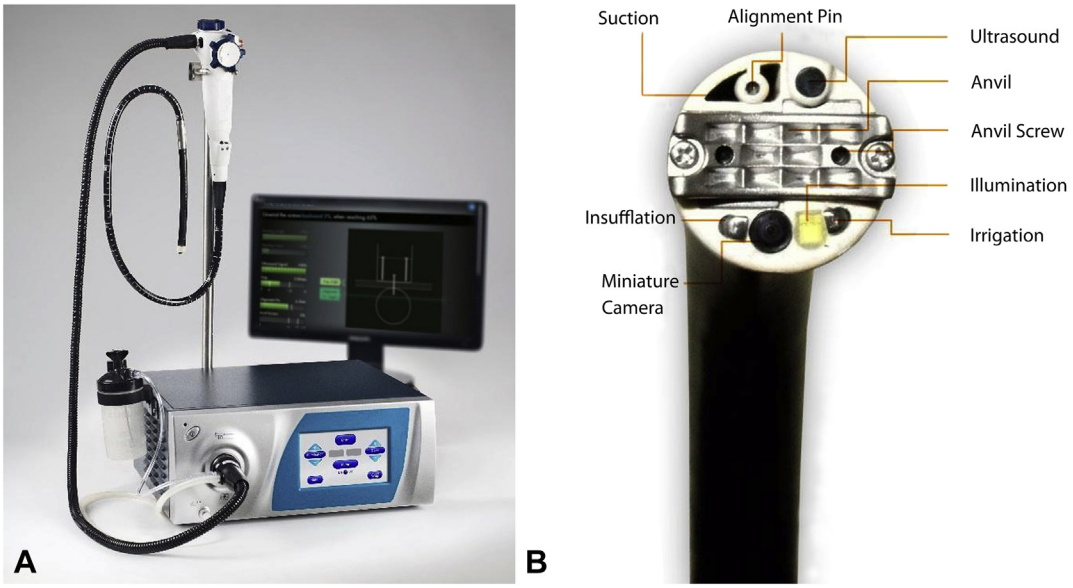

Figure 4. A, MUSE console and **(B)** tip of the endoscope (Medigus Ltd, Omer, Israel).

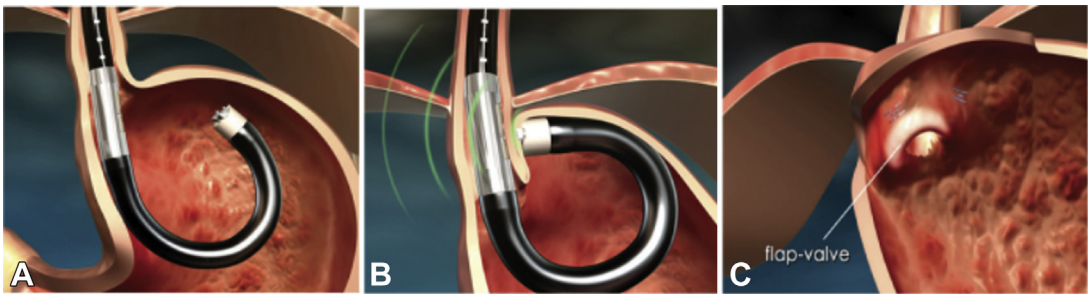

Figure 5. MUSE procedure. **A,** retroflexion. **B,** stapling. **C,** recreated GE junction (Medigus Ltd, Omer, Israel).

Another multicenter, randomized clinical trial (TEMPO) compared the efficacies of the TIF 2.0 procedure versus high-dose PPI therapy in patients with small hiatal hernias (≤2 cm) and abnormal esophageal acid exposure (confirmed by ambulatory pH monitoring 7 days after discontinuation of PPI therapy).[10] The primary endpoint of the study was elimination of daily troublesome reflux symptoms. At the end of a 6-month follow-up, esophageal acid exposure was normalized in 54% of patients (24 of 39) undergoing TIF, versus 52% of patients (11 of 21) on continuous high-dose PPI therapy ($P = .91$).[10] Elimination of troublesome GERD symptoms other than heartburn was observed in 62% (24 of 39) of patients in the TIF group compared with 5% of patients (1 of 21) on high-dose PPI therapy ($P < .01$), and 90% (35 of 39) of TIF patients were able to entirely discontinue PPI therapy. After completion of the clinical trial, TIF was offered to the PPI group patients who still had troublesome regurgitation despite PPI therapy.[11] All patients in the control group elected to undergo the TIF procedure (n = 21). In this crossover group, 6 months after the TIF procedure, 67% (6 of 9) of patients previously experiencing troublesome regurgitation achieved elimination of regurgitation and extraesophageal symptoms, and 71% (15 of 21) of patients were able to stop PPI treatment.[11] Analysis of objective parameters of regurgitation revealed that both TIF and high-dose PPI therapy reduced the number of reflux episodes, the percentage of time that esophageal pH was <4, and the DeMeester score (all P values < .01).[9]

Håkansson et al[12] randomized 44 patients with GERD receiving chronic PPI treatment to the TIF 2.0 procedure (n = 22) or to a sham procedure consisting of an upper GI endoscopy under general anesthesia (n = 22). The primary endpoint of the study was the time to treatment failure during the first 6 months after intervention. In this trial, 59% (13 of 22) of patients in the TIF group were off daily PPI therapy at 6 months, compared with 18% (4 of 22) of patients in the sham group ($P = .01$).[12]

Witteman et al[13] randomized 60 patients with GERD controlled with PPIs in a 2:1 ratio to either the TIF 2.0 procedure with discontinuation of PPIs or to continuation of PPIs. The primary endpoint of the study was improvement in GERD symptoms. Forty patients

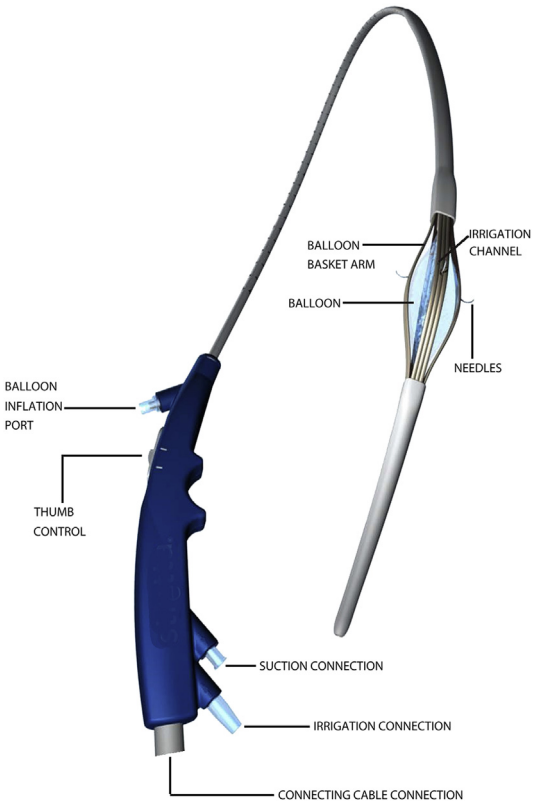

Figure 6. Stretta catheter (Mederi Therapeutics, Greenwich, Conn).

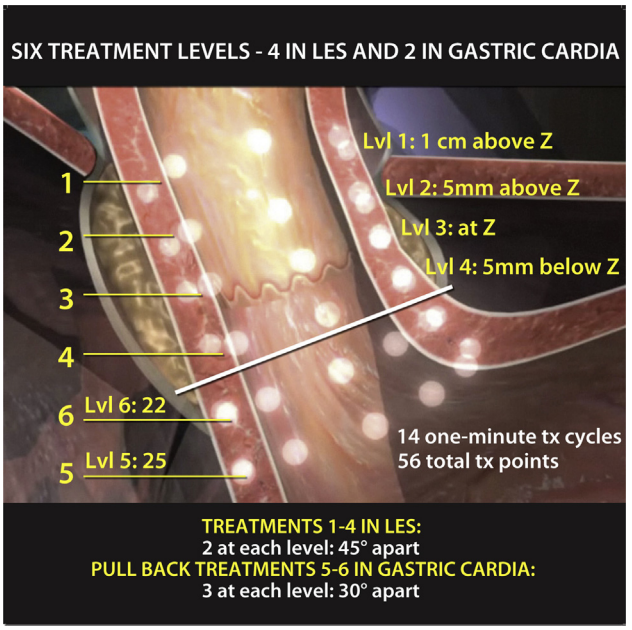

Figure 7. Stretta treatment levels (Mederi Therapeutics, Greenwich, Conn). *LES,* lower esophageal sphincter; *Lvl,* level; *tx,* treatment.

were randomized to the TIF 2.0 procedure, and 20 patients were continued on PPI treatment. At the 6-month follow-up, the GERD–health-related quality of life (HRQL) score improved in 55% (20 of 37) of patients in the TIF group compared with 5% (1 of 20) of patients on PPI therapy ($P < .01$).[13,14] All patients receiving PPI treatment opted for crossover at 6 months. However, at the 12-month follow-up, of the patients who initially underwent TIF, normalization of pH was accomplished in only 13 of 45 patients (29%), and 61% (38 of 45) of patients were back on PPI treatment.[13] The authors concluded that, although TIF resulted in a short-term improvement in the anti-reflux barrier, no long-term reflux control was achieved, and the study was terminated early after interim analysis.[13]

Systematic review. A systematic review included 15 studies (4 studies with TIF 1.0 procedure and 11 studies with TIF 2.0), with a total of 559 procedures, and the primary endpoint was to examine the effect of TIF on subjective and objective GERD indices. This review reported improvement in GERD-HRQL (21.9 baseline vs 5.9 post-TIF; $P < .01$) and the reflux symptom index (24.5 baseline vs 5.4 post-TIF; $P < .01$) scores after TIF.[14,15] Overall patient satisfaction was 72%, and the overall rate of PPI discontinuation was 67% across all studies, at a mean follow-up of 8.3 months. However, objective pH metrics such as the DeMeester score, mean acid exposure time, and number of reflux events did not consistently normalize across all studies.[9]

Long-term efficacy. Testoni et al[16] prospectively followed 50 patients who had undergone the TIF 2.0 procedure. All patients completed GERD-HRQL and GERD–health-related quality of life (GERD-QUAL) questionnaires and underwent upper GI endoscopy, esophageal manometry, and 24-hour pH-impedance at baseline and at 6, 12, and 24 months after TIF as well as subsequent yearly clinical evaluations.[14,16,17] At the time of publication, 32 patients had completed 3 years of follow-up, and 14 patients had completed 6 years of follow-up. Analysis of objective parameters showed no significant change in LES pressure and distal esophageal amplitude after TIF at 6, 12, and 24 months compared with baseline.[16] However, impedance monitoring showed significantly fewer total reflux events and acid reflux events after TIF treatment at 6, 12, and 24 months of follow-up. GERD-related symptom scores were significantly better compared with baseline at 6-, 12-, 24-, and 36-month follow-up. At the 3-year follow-up, 53% (17 of 32) of patients were off of PPI, and an additional 31% (10 of 32) had halved their PPI treatments. At the 6-year follow-up, 36% (5 of 14) of patients were off PPIs, and an additional 50% (7 of 14) had halved their PPI treatments.[16]

MUSE

The clinical efficacy of the MUSE procedure has been evaluated in a single prospective multicenter international trial and subsequent long-term follow-up study (Table 2).[18] At 6-months follow-up, GERD-HRQL scores improved by >50% in 73% (48 of 66) of patients, and 65% (42 of 66) of the patients were no longer using PPIs daily.[14,18] The mean percentage of total time with esophageal pH <4.0

TABLE 1. Summary of clinical studies on TIF

Study	Design	Intervention			
Hunter[7]	Prospective randomized multicenter sham-controlled study Total N = 129 Inclusion criteria Troublesome regurgitation (as per Montreal Protocol)[8] on PPIs (minimum 40 mg daily) Exclusion criteria Barrett's esophagus >2 cm Hiatal hernia >2 cm in either dimension Esophagitis LA grade[19] C or D Esophageal dysmotility Previous esophageal or gastric surgery Gastric outlet obstruction Gastroparesis Pregnancy or plans for pregnancy in next 12 mo. Immunosuppression Portal hypertension Coagulopathy BMI >35	TIF, followed by 6 mo. of placebo N = 87	Subjective outcome measures	Baseline	After 6 mo.
			Mean heartburn score	2.6	0.5
			Mean regurgitation score	3.5	0.5
			Mean heartburn and regurgitation score	3.1	0.6
			Elimination of troublesome regurgitation	–	54/81 (67%)
			Objective outcome measures		
			No. of reflux episodes	135	94
			Median 24-h pH (% time <4)	9.3	6.4
			DeMeester score[9]	33.6	23.9
		Sham procedure, followed by 6 mo. of PPIs N = 42	Subjective outcome measures		
			Mean heartburn score	3.0	0.8
			Mean regurgitation score	3.8	0.8
			Mean heartburn and regurgitation score	3.3	0.9
			Elimination of troublesome regurgitation	–	17/38 (45%)
			Objective outcome measures		
			No. of reflux episodes	125	122
			Median 24-h pH (% time <4)	8.6	8.9
			DeMeester score[9]	30.9	32.7
Trad[11]	Prospective randomized multicenter crossover study Total N = 63 Inclusion criteria Daily regurgitation or atypical symptoms (Montreal criteria)[8] on PPI Abnormal 48-h ambulatory pH test H/O daily PPI use for at least 6 mo. Exclusion criteria Barrett's esophagus >2 cm Hill grade[20] valve III or IV Hiatal hernia >2 cm in either dimension LA grade[19] C or D BMI >35	TIF N = 40	Subjective outcome measures	Baseline	After 6 mo.	After 12 mo.
			Resolution of regurgitation and atypical symptoms	–	13/20 (65%)	30/39 (77%)
			Mean GERD-HRQL score[14]	26.25	5.23	5.41
			Mean RDQ score[21]	2.91	0.35	0.50
			Mean RSI score[22]	22.00	4.64	4.79
			Objective outcome measures			
			Normalized esophageal pH	–	21/39 (54%)	17/38 (45%)
			Mean DeMeester score[9] (48-h pH study)	35.28	23.64	25.32
			Healed esophagitis	–	18/20 (90%)	19/19 (100%)
			PPI use			

(*continued on the next page*)

TABLE 1. Continued

			PPI use (daily/ occasional/none)	40/0/0 (100%/0/0)	1/3/36 (2%/8%/ 90%)	1/5/33 (3%/15%/ 82%)
		High dose PPI for first 6 mo., followed by TIF N = 23	Subjective outcome measures			
			Resolution of regurgitation and atypical symptoms	–	1/21 (5%)	6/9 (67%)
			Mean GERD-HRQL score[14]	26.43	18.86	10.05
			Mean RDQ score[21]	3.04	2.14	1.33
			Mean RSI score[22]	22.62	19.62	8.76
			Objective outcome measures			
			Normalized esophageal pH	–	11/21 (52%)	7/21 (33%)
			Mean DeMeester score[9] (48 hr pH study)	35.79	19.29	28.60
			Healed esophagitis	–	5/13 (38%)	11/13 (85%)
			PPI use			
			PPI use (daily/ occasional/none)	23/0/0 (100%/0/0)	23/0/0 (100%/0/0)	NA
Håkansson[12]	Prospective randomized double-blind sham-controlled study Total N = 44 Inclusion criteria On daily PPIs for >6 mo. Documented PPI dependency Persistent GERD symptoms without PPI therapy during the titration phase of the study Evidence of 2 or more of the following while off PPI therapy (>10 days): Erosive esophagitis (LA grade[19] A-C) Abnormal ambulatory pH study Moderate to severe GERD symptoms Normal or near normal esophageal motility (by manometry) Exclusion criteria Hiatal hernia >3 cm Esophagitis LA grade[19] D Esophageal ulcer Esophageal stricture Barrett's esophagus (Prague: C >1, M >2) Esophageal motility disorder Severe gastric paralysis Pregnancy or plans for pregnancy in the next 12 mo. Immunosuppression	TIF N = 22	Subjective outcome measures	Baseline		After 6 mo.
			QOLRAD estimates[23] (range)	4.9 (1.96-6.44)		6.4 (4.38-7)
			Median GSRS score (range)	14 (10-21)		10 (6-19)
			Objective outcome measures			
			Average time in remission	–		197 days
			Median 24-h pH (% time <4.2)	7.8		3.6
			Normalized 24-h pH study	–		20%
			Hill grading[20] of GE junction (I/II/III/IV)	0/4/11/0		4/8/3/0
			PPI use stopped	–		13/22 (59%)
		Sham procedure N = 22	Subjective outcome measures	Baseline		After 6 mo.
			QOLRAD estimates[23] (range)	4.8 (1.80-6.44)		5.2 (4.28-6.88)
			Median GSRS score[24] (range)	14.0 (6.3-21.8)		12.6 (5.9-21.2)
			Objective outcome measures			

(*continued on the next page*)

TABLE 1. Continued

	ASA >2 Portal hypertension and/or varices History of previous resective gastric or esophageal surgery, cervical spine fusion, Zenker's diverticulum, esophageal epiphrenic diverticulum, achalasia, scleroderma or dermatomyositis, eosinophilic esophagitis, or cirrhosis Active gastroduodenal ulcer disease Gastric outlet obstruction or stenosis Severe gastroparesis or delayed gastric emptying Coagulation disorders BMI >35		Average time in remission	–	107 days
			Median 24-h pH (% time <4.2)	13.1	9.8
			Normalized 24-h pH study	–	20%
			Hill grading[20] of GE junction (I/II/III/IV)	1/2/11/0	1/2/5/2
			PPI use stopped	–	4/22 (18%)
Witteman[13]	Two-center randomized crossover study (without sham) Total N = 60 Inclusion criteria Proven gastroesophageal reflux (pH <4 for >4.3% time while off PPIs for 7-14 days) On daily PPIs for >1 year Recurrence of GERD symptoms (GERD-HRQL score[14] difference of >10 between on and off PPIs) Normal or hypotonic LES resting pressure (5-40 mmHg) Exclusion criteria Hiatal hernia >2 cm Esophagitis grade D Barrett's esophagus Esophageal stricture Esophageal ulcer Esophageal motility disorder Gastric motility disorder Prior splenectomy Gastric paralysis Pregnancy Immunosuppression ASA >2 Portal hypertension Coagulation disorders Previous anti-reflux procedure BMI >35	TIF 2.0 (EsophyX-2 device with SerosaFuse fasteners) N = 40	Subjective outcome measures	Baseline	After 6 mo.
			Mean GERD-HRQL score[14]	26.5	12.4
			% with >50% improvement in GERD-HRQL score[14]	–	20/37 (55%)
			Objective outcome measures		
			Median 24-h pH (% time <4)	10.8	7.7
			Median no. of reflux episodes	111	78
			Median LES resting pressure mmHg	15.2	18.2
			% with esophagitis	13/40 (33%)	5/37 (14%)
			PPI use		
			PPI use (none/occasional/daily single dose/daily double dose)	0/0/40/0 (0/0/100%/0)	28/6/3/0 (74%/17%/9%/0%)
		Six mo. of PPI followed by option to undergo TIF 2.0 N = 20	Subjective outcome measures		
			Mean GERD-HRQL score[14]	28.2	25.1
			% with >50% improvement in GERD-HRQL score[14]	–	1/20 (5%)
			Objective outcome measures		
			Median 24-h pH (% time <4)	11.3	6.0
			Median no. of reflux episodes	109	101
			Median LES resting pressure mmHg	15.5	13.6
			% with esophagitis	6/20 (30%)	2/20 (10%)
			PPI use		

(*continued on the next page*)

TABLE 1. Continued

		PPI use (none/occasional/daily single dose/daily double dose)	0/0/20/0 (0/0/100%/0)	0/0/18/2 (0/0/90%/10%)
Pooled data from both groups, after crossover N = 53	Subjective outcome measures	Baseline	6 mo. after TIF	12 mo. after TIF
	Mean GERD-HRQL score[14]	27.1	11.1	10.3
	Objective outcome measures			
	Mean 24-h pH (% time <4)	11.0	7.9	9.1
	Median LES resting pressure mmHg	15.3	17.8	17.6
	PPI use			
	PPI use (none/occasional/daily single dose/daily double dose)	0/0/60/0 (0/0/100%/0)	35/10/6/2 (66%/19%/11%/4%)	(n = 45) 17/8/16/4 (39%/17%/36%/8%)

PPI, Proton pump inhibitor; *TIF,* transoral incisionless fundoplication; *LA,* Los Angeles; *BMI,* body mass index; *H/O,* history of; *HRQL,* health-related quality of life; *RDQ,* Roland-Morris Disability Questionnaire; *RSI,* reflux symptom index; *NA,* not available; *QOLRAD,* quality of life in reflux and dyspepsia; *GSRS,* Gastrointestinal Symptom Rating Scale; *GE,* gastroesophageal; *LES,* lower esophageal sphincter.
$EsophyX_2$ (EndoGastric Solutions, Redmond, Wash).
SerosaFuse fasteners (EndoGastric Solutions, Redmond, Wash).

decreased significantly at 6 months compared with baseline (from 10.9 to 7.3; $P < .001$). Long-term follow-up was subsequently reported for 37 patients enrolled in the initial clinical trial. At 4-year post-procedure follow-up, 69.4% of patients (25 of 36) were off daily PPI.[25] The GERD-HRQL score was significantly decreased from baseline (29.1 ± 5.6) at 6-month (8.9 ± 8.3; $P < .01$) and 4-year follow-up (5.3 ± 5.8).[14,25]

Stretta

Randomized clinical trials. Four randomized clinical trials have evaluated the Stretta device for the treatment of GERD (Table 3). Corley et al[26] conducted a randomized controlled trial on 64 patients, comparing the Stretta procedure (n = 35) to a sham procedure (n = 29), with follow-up for 6 months. Primary endpoints of the study were GERD symptoms and improvement in the quality of life. At the 6-month follow-up, there was no difference in PPI usage (17 of 31 [55%] vs 14 of 23 [61%]; $P = .67$) or in median esophageal acid exposure time reductions (-1.8 vs -1.5; $P = .79$) between the Stretta and sham groups.[26] However, patients receiving the Stretta procedure reported significant improvements in both symptomatic relief (19 of 31 [61%] vs 7 of 21 [33%]; $P = .05$) and HRQL scores (19 of 32 [61%] vs 6 of 21 [30%]; $P = .03$) compared with those receiving the sham procedure.[26]

Coron et al[27] randomized 43 PPI-dependent patients to the Stretta procedure (23 patients) or to PPI treatment (20 patients). The primary endpoint of the study was to stop or decrease PPI use by >50%. Intention-to-treat analysis at the 6-month endpoint revealed that 78% (18 of 23) of patients in the Stretta group were able to reduce PPI intake by more than 50%, compared with 40% (8 of 20) of patients in the control arm ($P = .01$).[27] However, this improvement was not sustained at 12 months of follow-up, with only 56% (13 of 23) of patients in the Stretta group able to discontinue or decrease PPI use versus 35% (7 of 20) of patients in the control group ($P = .16$). This study failed to demonstrate any significant difference in HRQL assessment (measured by the REFLUX-QUAL [Quality of Life Questionnaire in Gastroesophageal Reflux] questionnaire[19] and a 36-item short-form health survey[20]) between the 2 groups at 6-month and 12-month periods.[27-29]

Aziz et al[30] conducted a 3-arm randomized controlled trial comparing a single Stretta procedure and double Stretta procedures with a sham procedure (n = 12 in each arm, total = 36). Among the patients randomized to the double Stretta arm (n = 12), a second RF procedure was performed only on patients who did not show an improvement of more than 75% in HRQL at 4-months follow-up after the first Stretta procedure (n = 10).[30] At 12 months of follow-up, the mean HRQL scores, LES basal pressure, 24-hour pH scores, and daily PPI use were significantly improved compared with baseline in both single and double Stretta groups ($P < .01$).[30] Both single and double Stretta treatment groups showed significant improvement in mean HRQL scores compared with sham treatment ($P < .05$ and $P < .01$, respectively).[30]

TABLE 2. Summary of clinical studies on MUSE

Study	Design	Intervention				
Zacherl[18]	Multicenter, randomized open label trial Total N = 66 Inclusion criteria H/O GERD-related symptoms ≥2 years Abnormal 24-h pH acid exposure test result H/O daily PPI ≥6 mo., with significant relief of symptoms (ie, difference in GERD HRQL scores[14] on and off PPIs ≥6) GERD-HRQL[14] ≥20 off of PPIs Exclusion criteria Hiatal hernia >3 cm Paraesophageal hernia Barrett's esophagus Grade IV esophagitis[20] Esophageal stricture, ring or web causing symptoms of dysphagia Grade I flap valve according to Hill classification[20] H/O comorbidity	MUSE N = 66	Subjective outcome measures	Baseline (on PPI)	Baseline (off PPI)	6 mo. after MUSE
			Mean GERD-HRQL score[14]	14.9	29.7	9.0
			% with >50% improvement in GERD-HRQL score[14]	–	–	48/66 (73%)
			Mean heartburn score	11.0	21.9	7.2
			Objective outcome measures			
			Mean 24-h pH (% time <4)	–	10.9 (N = 66)	7.3 (N = 64)
			Median LES pressure (mmHg)			
			PPI use			
			Mean dose mg/day	58.5 (n = 65)	–	42/65 (64.6%)
Kim[25]	Long-term follow-up of cohort above	MUSE	Subjective outcome measures	Baseline (off PPI)	6 mo. after MUSE	4 years after MUSE
			Mean GERD-HRQL score	29.1	8.9	5.3
			Objective outcome measures			
			Mean 24-h pH (% time <4)	NA	NA	NA
			Median LES pressure (mmHg)	NA	NA	NA
			PPI use			
			% of patients off PPI		31/37 (83.8%)	25/36 (69.4%)

MUSE, Medigus Ultrasonic Surgical Endostapler; *PPI,* proton pump inhibitor; *HRQL,* health-related quality of life; *H/O,* history of; *LES,* lower esophageal sphincter; *NA,* not available.
MUSE (Medigus Ltd, Omer, Israel)

Arts et al[6] randomized 22 patients to either the Stretta procedure or to a sham procedure. There were no significant differences in esophageal acid pH exposure times (8.8 ± 6.1 vs 11.4 ± 6.3; $P = .11$) or reduction in PPI use (13 of 23 [56%] vs 7 of 20 [35%]; $P = .16$) between the Stretta and sham procedures.[6] However, 3 months after the Stretta procedure, the quality of life score for bodily pain was significantly improved compared with the pretreatment score (49.5 ± 9.5 vs 24 ± 4.3; $P < .05$).[6] The study also assessed LES distensibility by using a barostat bag. A decrease in LES compliance was noted after the Stretta procedure (17.8 ± 3.6 vs 7.4 ± 3.4 mL/mm Hg; $P < .05$), which was found to be reversible on local administration of sildenafil (14.9 ± 3.8 mL/mm Hg).[6] The study suggested that decreased LES compliance after the Stretta procedure is likely related to altered LES neuromuscular function rather than LES fibrosis.[6]

Systematic review and meta-analysis. Perry et al[31] conducted a systematic review and meta-analysis on the efficacy of the Stretta procedure including 1441 patients from 18 studies (2 randomized controlled trials and 16 cohort studies). They concluded that RF treatment improved heartburn scores and the GERD-HRQL score.[31] Johnson-DeMeester scores also decreased from a preprocedure level of 44.4 to 28.5 ($P < .01$) after the procedure.[9,31]

Lipka et al[32] conducted another systematic review and meta-analysis that included 165 patients from 4 randomized controlled trials, comparing the Stretta procedure to either a sham procedure or to PPI therapy. In contrast to the meta-analysis performed by Perry et al,[31] the meta-analysis by Lipka et al[32] found no difference between the Stretta versus sham groups or Stretta versus management with PPI groups for the outcomes of mean (%) amount of time the esophageal pH was <4 over a 24-hour time

TABLE 3. Summary of clinical studies on Stretta

Study	Design	Intervention				
Corley[26]	Multicenter randomized, double-blinded, controlled trial Total N = 64 Inclusion criteria Heartburn or reflux on daily PPI 24-hour pH study (off medications) showing abnormal esophageal acid exposure (≥4%) or a DeMeester score[9] of ≥14.7 Normal esophageal peristalsis and sphincter relaxation Esophagitis (by EGD) Savary-Miller[33] grades I and II or absent Exclusion criteria Hiatal hernia >2cm Presence of Barrett's esophagus Savary-Miller[33] III and above Unstable general condition Coagulopathy	Stretta, followed by PPI for 21 days N = 35	Subjective outcome measures	Baseline	After 6 mo.	
			Mean heartburn score	3.8	2.2	
			Mean HRQL score[14]	28	16	
			Mean SF-36 physical score[29]	40	47	
			Objective outcome measures			
			Median 24-h pH (% time < 4)	9.5	9.9	
			LES pressure in mmHg	13	16.2	
			Esophageal erosions	4 (11%)	5 (19%)	
			PPI use			
			Daily use	30 (88%)	13 (42%)	
		Sham procedure followed by 6 months of PPI, then 20 patients opted for Stretta with follow-up 6 mo. later. N = 29 with crossover = 20	Subjective outcome measures			
			Mean heartburn score	3.6	2.8	
			Mean HRQL score[14]	25	21	
			Mean SF-36 physical score[29]	42	42	
			Objective outcome measures			
			Median 24-h pH (% time <4)	9.9	10.7	
			LES pressure in mmHg	12.1	18	
			Esophageal erosions	6	5	
			PPI use			
			Daily use	21 (72%)	10 (29%)	
Coron[27]	Multicenter randomized, double-blinded, controlled trial (without sham procedure) Total N = 43 Inclusion criteria Reflux controlled with at least standard dose 24-hour pH study (off medications) showing abnormal esophageal acid exposure (≥ 4%) Normal esophageal peristalsis and sphincter relaxation Esophagitis by EGD LA classification[19] A or B or absent Exclusion criteria Patients whose symptoms are adequately relieved with half-dose PPI regimen or intermittent acid suppression Presence of Barrett's esophagus >3 cm and/or with dysplasia and/or previously treated Hiatal hernia >3 cm	Stretta N = 23	Subjective outcome measures	Baseline	After 6 mo.	After 12 mo.
			Mean heartburn score	1.6 ± 0.7	2.1 ± 1.0	1.7 ± 0.8
			Mean regurgitation score	1.6 ± 1.0	1.3 ± 0.6	1.2 ± 0.4
			Mean SF-36 physical score[29]	49 ± 7	48 ± 8	53 ± 7
			Mean REFLUX-QUAL[28] global score	67 ± 20	75 ± 21	84 ± 9
			Objective outcome measures			
			Median 24-h pH (% time <4)	12.2 ± 7.1	11.4 ± 6.3	NA
			No. of reflux episodes >5 min	7 ± 5	7 ± 6	NA
			Esophagitis	8/23 (35%)	10/19 (53%, 1 patient declined EGD)	NA
			Daily PPI use			
			Stopped or decreased >50% of earlier dose	–	18/23 (78% ITT), 18/20 (90% PP)	13/23 (56% ITT), 13/20 (65% PP)

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TABLE 3. Continued

	LA grade[19] C or D Presence of esophageal stricture or achalasia H/O esophageal or gastric surgery Presence of gastric or esophageal varices Presence of a cardiac pacemaker or any other implanted electro-medical device Severe coagulopathy Any contraindication to general anesthesia Life-threatening disorders with a life expectancy of <1 year High alcohol consumption (>60 g/day) Morbid obesity (BMI >35)		Completely stopped PPI	–	3/23 (13% ITT), 3/20 (15% PP)	4/23 (17% ITT), 4/20 (20% PP)
		Control arm, maintained on PPI (no sham procedure) N = 20	Subjective outcome measures			
			Mean heartburn score	1.3 ± 0.6	2.4 ± 1.4	2.3 ± 1.5
			Mean regurgitation score	1.2 ± 0.5	2.2 ± 1.3	1.7 ± 1.4
			Mean SF-36[29] physical score	46 ± 7	49 ± 7	40 ± 10
			Mean REFLUX-QUAL[28] global score	68 ± 16	68 ± 21	77 ± 18
			Objective outcome measures			
			Median 24-h pH (% time <4)	12.1 ± 10.7	8.8 ± 6.1	NA
			No. of reflux episodes >5 min	6 ± 6	4 ± 4	NA
			Esophagitis	5/20 (25%)	7/13 (54%, 4 patients declined EGD)	NA
			Daily PPI use			
			Stopped or decreased >50% of earlier dose		8/20 (40% ITT), 8/16 (50% PP)	7/20 (35% ITT), 6/16 (38% PP)
			Completely stopped PPI		0	0
Aziz[30]	Single-center randomized, double-blinded, controlled trial Total N = 36 Inclusion criteria Heartburn, regurgitation, or both for >6 mo. GERD-HRQL[14] >18 (off medications ≥10 days) GERD-HRQL[14] >10 (on medications) Daily PPI with partial response 24-h pH <4 for >4.2% of time Esophagitis (by EGD) LA Classification[19] A or B or absent Exclusion criteria Sliding hiatal hernia >2 cm Presence of Barrett's dysplasia Esophagitis (by EGD) LA classification[19] C or D H/O esophageal and/or gastric surgery Poor surgical candidates Collagen vascular diseases Autoimmune disorders Pregnancy	Sham procedure N = 12	Subjective outcome measures	Baseline	After 12 mo.	
			Mean HRQL score (off medications)	30.3 ± 3.8	24.8 ± 4.9	
			No. of patients with HRQL[14] ≤11	0	0	
			Objective outcome measures			
			No. of patients with normalized 24-h pH study	0	0	
			LES pressure mmHg	14.1 ± 2.6	15.9 ± 3.2	
			Esophagitis (normal/A/B)	3/6/3	3/5/4	
			24-h pH monitoring (% time <4.2)	9.9 ± 3.8	8.2 ± 3.1	
			PPI use			
			Patients off medications	-	0	
		One session of Stretta N = 12	Subjective outcome measures			
			Mean HRQL[14] score (off medications)	29.6 ± 3.9	14.4 ± 4.8	
			No. of patients with HRQL ≤11	0	2	
			Objective outcome measures			
			No. of patients with normalized 24-h pH study	0	5	
			LES pressure mmHg	11.6 ± 3.2	16.2 ± 4.5	
			Esophagitis (normal/A/B)	0/9/3	4/8/0	
			24-h pH monitoring (% time <4.2)	9.4 ± 3.4	6.7 ± 2.8	

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TABLE 3. Continued

			PPI use		
			Patients off medications	–	2
		One session of Stretta followed by second session at 4 mo., if improvement in GERD-HRQL[14] <75%, and follow-up for 12 mo. subsequently N = 10/12	Subjective outcome measures		
			Mean HRQL score (off medications)	31.0 ± 4.9	10.7 ± 9.6
			No. of patients with HRQL[14] ≤11	0	7*
			Objective outcome measures		
			No. of patients with normalized 24-h pH study	0	7*
			LES pressure mmHg	12.2 ± 3.7	19.6 ± 2.9*
			Esophagitis (normal/A/B)	4/4/4	7/5/0*
			24-h pH monitoring (% time <4.2)	8.8 ± 2.8	5.2 ± 2.4*
			PPI use		
			Patients off medications	–	7*
			*12 mo. after second session of Stretta		
Arts[6]	Randomized, double-blinded, controlled trial Total N = 22 Inclusion criteria Long-standing H/O GERD with typical symptoms 24-h pH <4 for >4% of time Complete or partial response to high-dose PPI Modified Savary-Miller classification[33] 1 or 2 or LA classification A or B Exclusion criteria Large hiatal hernia >3 cm Modified Savary-Miller classification[33] 3 or 4 or LA classification C or D Absent peristaltic contractions on manometry Coagulopathy	Stretta followed by sham procedure at 3 mo. N = 11	Subjective outcome measures	Baseline	3 mo. after Stretta	6 mo. after Stretta
			GERD symptom score	14.7 ± 1.5	8.3 ± 1.9	7.8 ± 2.1
			SF-36 physical functioning score	56.7 ± 13.4	73.8 ± 9.3	65.6 ± 12.0
			Objective outcome measures			
			LES resting pressure mmHg	11.9 ± 1.2	13.3 ± 1.9	13.7 ± 2.2
			Esophagitis	–	NSC	NSC
			24-h pH monitoring (% time <4)	–	NSC	NSC
			PPI use			
			Tablets/mo.	32.0 ± 4.8	33.3 ± 2.9	32.5 ± 7.0
		Sham procedure followed by Stretta at 3 mo. N = 11	Note: 6 mo. after Stretta is the same as 3 mo. after sham			
			Subjective outcome measures	Baseline	3 mo. after sham	3 mo. after crossover (Stretta)
			GERD symptom score	16.1 ± 2.5	15.6 ± 2.2	7.2 ± 1.6
			SF-36 physical functioning score	57.5 ± 6.4	76.1 ± 5.6	80.5 ± 6.0
			Objective outcome measures			
			LES resting pressure mmHg	15.6 ± 2.1	16.3 ± 2.0	15.2 ± 3.5
			Esophagitis	–	NSC	NSC
			24-h pH monitoring (% time <4)	–	NSC	NSC
			PPI use			
			Tablets/mo.	32.1 ± 3.5	24.0 ± 3.0	24.1 ± 5.7

PPI, Proton pump inhibitor; *HRQL,* health-related quality of life; *SF-36,* Short-Form Health Survey; *LES,* lower esophageal sphincter; *REFLUX-QUAL;* Quality of Life Questionnaire in Gastroesophageal Reflux; *N/A,* not applicable; *ITT,* intention to treat; *PP,* per protocol; *H/O,* history of; *BMI,* body mass index; *LA,* Los Angeles; *NSC,* no significant changes.
DeMeester scale.
Savary-Miller grade.
SF-36 scale.
LA grade.
REFLUX-QUAL scale.

course, LES pressure, ability to stop PPI therapy, or GERD-HRQL.[31] A likely reason for the discrepancy between the 2 meta-analyses is the number of included studies and the total number of patients as well as variation in study design and primary outcome between the randomized trials.

Long-term efficacy. Two single-arm prospective trials have evaluated long-term efficacy data for the Stretta procedure.[34,35] Dughera et al[34] performed the Stretta procedure on 86 patients between 2002 and 2013. Patients underwent upper endoscopy, esophageal manometry, and pH studies at baseline, 4 years, and 8 years. At the time of analysis, 26 patients had completed 8 years of follow-up. No difference in median LES pressure was noted after the procedure. The mean esophageal acid exposure significantly improved at 4 years ($P < .01$) but returned to baseline values at 8 years of follow-up.[34] Significant improvement in both heartburn (mean decrease -2.8 points; $P = .001$ and -1.8 points; $P = .003$) and GERD-HRQL (mean decrease -14 points; $P = .001$ and -11 points; $P = .003$) scores were noted compared with baseline, at 4 years, and at 8 years, respectively.[34] Over the course of the follow-up, 21 of 26 (80.7%; $P < .01$) patients were completely off PPI treatment at 4 years, as were 20 of 26 (76.9%, $P < .01$) patients at 8 years.[34] Noar et al[35] prospectively evaluated 217 patients with GERD refractory to medical therapy and reported 10-year follow-up results after the Stretta procedure as an intent-to-treat analysis. Of the 99 patients completing a 10-year follow-up, 72% had normalization of GERD-HRQL, and 41% were able to discontinue PPI therapy.[36]

SAFETY

TIF

Postprocedure adverse events such as throat pain, cough, nausea, dysphagia, chest pain, epigastric abdominal pain, and musculoskeletal pain have been reported in clinical trials.[7,12,13] A systematic review of 559 procedures (from 15 studies) reported 18 adverse events requiring either therapeutic intervention or prolonged hospitalization.[15] In this review, the most common adverse events were hemorrhage in 6 patients (1.1%) and esophageal perforation in 4 patients (0.7%). Other rare reported adverse events included hematoma, mediastinal abscess, hematemesis, pneumothorax, aspiration pneumonia, and permanent tongue numbness.[15] A case of pneumoperitoneum requiring needle decompression during the TIF procedure also has been reported.[13]

MUSE

In a multicenter trial, 8 serious adverse events were reported in the first 24 patients undergoing the procedure, including pain, fever, viral infection, and pneumomediastinum and/or pneumoperitoneum.[18] Two severe adverse events that were reported included an esophageal leak resulting in pneumothorax and empyema in a patient, requiring a chest tube, antibiotics, and 22 days of hospitalization, and upper GI bleeding in another patient requiring the transfusion of 2 units of blood.[18] Interim review of these early serious adverse events resulted in protocol and device changes. Six of the 8 serious adverse events occurred in patients who received stapling at only 2 sites, and therefore an additional stapling site was encouraged, with the aim of reducing stress at any individual stapling site.[18] Additionally, the protocol was amended to require prophylactic antiemetic therapy to prevent immediate postoperative retching, and a chest radiograph was obtained to exclude leaks before discharge.[15] Changes also were made in the device design to prevent air insufflation during screw insertion to prevent air leakage into the peritoneum.[18] After these changes, no cases of leakage or pneumomediastinum were noted in the subsequent 48 treated patients.

Stretta

Transient minor adverse events such as retrosternal and/or epigastric discomfort or pain, throat pain, mild fever, nausea and/or vomiting, odynophagia, and dysphagia have been observed in clinical trials.[6,26,27,30] Worsening of preexisting delayed gastric emptying was reported by Corley et al[26] in 1 (of 35) patient and by Aziz et al[30] in 2 (of 10) patients receiving double Stretta treatment. The meta-analysis by Perry et al[31] reported gastroparesis and ulcerative esophagitis to be the most common adverse events after Stretta. Triadafilopoulos[36] reported that 2774 patients have undergone Stretta as part of 32 clinical trials, and more than 15,000 patients have been treated with Stretta overall, with an overall reported adverse event rate of <1%. Lipka et al[32] performed a manufacturer and user facility device experience (MAUDE) database search and reported serious adverse events such as aspiration pneumonia, permanent gastroparesis, esophageal perforation, and cardiac arrest after the Stretta procedure. There were 4 reported deaths in the MAUDE database related to these adverse events.[32]

EASE OF USE

Need for specialized training

Endoscopic anti-reflux procedures are more challenging than routine diagnostic or therapeutic upper endoscopy. At present, there are no thresholds set by the ASGE or other endoscopic societies for establishing competency in performing these anti-reflux procedures. However, manufacturers of each device require endoscopists to complete specialized training before they can perform procedures with these devices. The manufacturers of the EsophyX device require dedicated training on a live canine model. Similarly, manufacturers of the MUSE device require dedicated training on live pig models. The manufacturers of

TABLE 4. Summary of accessory components and cost of each device

Technique	Equipment/device	Model/part no.	Cost
TIF	EsophyX$_2$ HD Device	R2005	$3575
	EsophyX Z Device	R2006	$3775
	SerosaFuse Implantable Fastener Cartridge (20 fasteners, 6.5 mm)	R2165	$425
	SerosaFuse Implantable Fastener Cartridge (20 fasteners, 7.5 mm)	R2175	$425
	SerosaFuse Implantable Fastener Kit (contains 1 EsophyX HD device, one 6.5-mm, and one 7.5-mm cartridge)	R2167	$4215
MUSE	MUSE Endostapler	MMAA 1006001	$3200
	Staple cartridge box (30 cartridges, 3 cartridges required for 1 procedure)	MMAA 9001011	$3150
	MUSE Console	MDVI 1800001	$47,500
Stretta	Mederi RF Generator (MDRF1 Stretta System)		$30,000
	Stretta catheter		$2700

TIF, Transoral incisionless fundoplication; *MUSE*, Medigus Ultrasonic Surgical Endostapler.
TIF, EsophyX device; EndoGastric Solutions, Redmond, Wash.
MUSE, Medigus Ultrasonic Surgical Endostapler; Medigus Ltd, Omer, Israel.
Stretta, Mederi Therapeutics, Greenwich, Conn.

Stretta require completion of online training followed by in-person training on use of the device in an ex vivo model.

FINANCIAL CONSIDERATIONS

The EsophyX device is a single-use device and does not require purchase of any additional equipment. The Stretta device requires purchase or a lease agreement for the RF generator, and the MUSE device requires purchase or a lease agreement for the MUSE console.

Reimbursement

The coding and reimbursement for endoscopic anti-reflux procedures have undergone recent changes, with dedicated current procedural terminology (CPT) codes now available for Stretta, TIF, and MUSE procedures. CPT code 43257 is used for Stretta treatment and includes flexible, transoral upper endoscopy with application of RF energy at the LES and/or gastric cardia. CPT code 43210 is effective since January 2016 and incorporates endoscopic fundoplication procedures including TIF and MUSE. Table 4 highlights the cost of each of the devices including the accessory components.

FUTURE RESEARCH

Large, randomized, well-designed, controlled trials are unlikely to be completed in the future. These devices could be compared with laparoscopic anti-reflux surgery in randomized controlled trials. Most current clinical trials have selected only 3-month or 6-month follow-up times to evaluate efficacy, and, thus, long-term post-market registries are needed while these devices are used clinically in centers of excellence to establish the safety and efficacy of these devices over a longer period.

SUMMARY

Endoscopic anti-reflux procedures offer a minimally invasive option for select patients with GERD not controlled by PPIs, with randomized trials showing a variable degree of improvement in patient-oriented outcomes such as GERD-HRQL scores and the ability to decrease or discontinue acid suppressive medication. Although results from current clinical trials have not shown consistent improvement in objective disease-oriented outcomes such as normalization of esophageal pH values and augmentation of LES pressure, patients do report subjective clinical improvement. Currently, use of these devices should be limited to dedicated anti-reflux centers with appropriate training and expertise to carefully evaluate patients with PPI-unresponsive GERD while offering them expanded medical, endoscopic, and surgical options for management.

DISCLOSURES

N. Thosani is a consultant for Boston Scientific, Medtronics, and Mederi Inc and is a speaker for Abbvie. U. Navaneethan is a member of the speaker bureau for Takeda and Janssen and is a consultant for Abbvie. S. Sullivan does consulting and contracted research for USGI Medical and Obalon Therapeutics. Dr Sullivan is also a consultant for Elira Therapeutics and

Enteromedics and is on the advisory board for Takeda Pharmaceuticals. Dr Sullivan also does contracted research for GI Dynamics, Aspire Bariatrics, Baronova, and Paion.

Abbreviations: ASGE, American Society for Gastrointestinal Endoscopy; CPT, Current Procedure Terminology; FDA, Food and Drug Administration; GEJ, gastroesophageal junction; HRQL, health-related quality of life; LES, lower esophageal sphincter; MAUDE, manufacturer and user facility device experience; MUSE, Medigus Ultrasonic Surgical Endostapler; PPI, proton pump inhibitor; QUAL, quality of life; RF, radiofrequency; TIF, transoral incisionless fundoplication.

REFERENCES

1. Peery AF, Crockett SD, Barritt AS, et al. Burden of gastrointestinal, liver, and pancreatic diseases in the United States. Gastroenterology 2015;149:1731-41; e3.
2. Katz PO, Gerson LB, Vela MF. Guidelines for the diagnosis and management of gastroesophageal reflux disease. Am J Gastroenterol 2013;108: 308-28; quiz 29.
3. Auyang ED, Carter P, Rauth T, et al. Sages Guidelines Committee. SAGES clinical spotlight review: endoluminal treatments for gastroesophageal reflux disease (GERD). Surg Endosc 2013;27: 2658-72.
4. Chey WD, Mody RR, Izat E. Patient and physician satisfaction with proton pump inhibitors (PPIs): Are there opportunities for improvement? Dig Dis Sci 2010;55:3415-22.
5. Broeders JA, Bredenoord AJ, Hazebroek EJ, et al. Reflux and belching after 270 degree versus 360 degree laparoscopic posterior fundoplication. Ann Surg 2012;255:59-65.
6. Arts J, Bisschops R, Blondeau K, et al. A double-blind sham-controlled study of the effect of radiofrequency energy on symptoms and distensibility of the gastro-esophageal junction in GERD. Am J Gastroenterol 2012;107:222-30.
7. Hunter JG, Kahrilas PJ, Bell RC, et al. Efficacy of transoral fundoplication vs omeprazole for treatment of regurgitation in a randomized controlled trial. Gastroenterology 2015;148:324-33.e5.
8. Vakil N, van Zanten SV, Kahrilas P, et al. The Montreal definition and classification of gastroesophageal reflux disease: a global, evidence-based consensus paper [German]. Z Gastroenterol 2007;45:1125-40.
9. Jamieson JR, Stein HJ, DeMeester TR, et al. Ambulatory 24-h esophageal pH monitoring: normal values, optimal thresholds, specificity, sensitivity, and reproducibility. Am J Gastroenterol 1992;87:1102-11.
10. Trad KS, Barnes WE, Simoni G, et al. Transoral incisionless fundoplication effective in eliminating GERD symptoms in partial responders to proton pump inhibitor therapy at 6 months: the TEMPO Randomized Clinical Trial. Surg Innov 2015;22:26-40.
11. Trad KS, Simoni G, Barnes WE, et al. Efficacy of transoral fundoplication for treatment of chronic gastroesophageal reflux disease incompletely controlled with high-dose proton-pump inhibitors therapy: a randomized, multicenter, open label, crossover study. BMC Gastroenterol 2014;14:174.
12. Håkansson B, Montgomery M, Cadiere GB, et al. Randomised clinical trial: transoral incisionless fundoplication vs. sham intervention to control chronic GERD. Aliment Pharmacol Ther 2015;42:1261-70.
13. Witteman BP, Conchillo JM, Rinsma NF, et al. Randomized controlled trial of transoral incisionless fundoplication vs. proton pump inhibitors for treatment of gastroesophageal reflux disease. Am J Gastroenterol 2015;110:531-42.
14. Velanovich V, Valiance SR, Gusz JR, et al. Quality of life scale for gastroesophageal reflux disease. J Am Coll Surg 1996;183:217-24.
15. Wendling MR, Melvin WS, Perry KA. Impact of transoral incisionless fundoplication (TIF) on subjective and objective GERD indices: a systematic review of the published literature. Surg Endosc 2013;27: 3754-61.
16. Testoni PA, Testoni S, Mazzoleni G, et al. Long-term efficacy of transoral incisionless fundoplication with Esophyx (TIF 2.0) and factors affecting outcomes in GERD patients followed for up to 6 years: a prospective single-center study. Surg Endosc 2015;29:2770-80.
17. Chan Y, Ching JY, Cheung CM, et al. Development and validation of a disease-specific quality of life questionnaire for gastro-oesophageal reflux disease: the GERD-QOL questionnaire. Aliment Pharmacol Ther 2010;31:452-60.
18. Zacherl J, Roy-Shapira A, Bonavina L, et al. Endoscopic anterior fundoplication with the Medigus Ultrasonic Surgical Endostapler (MUSE) for gastroesophageal reflux disease: 6-month results from a multi-center prospective trial. Surg Endosc 2015;29:220-9.
19. Lundell LR, Dent J, Bennett JR, et al. Endoscopic assessment of oesophagitis: clinical and functional correlates and further validation of the Los Angeles classification. Gut 1999;45:172-80.
20. Oberg S, Peters JH, DeMeester TR, et al. Endoscopic grading of the gastroesophageal valve in patients with symptoms of gastroesophageal reflux disease (GERD). Surg Endosc 1999;13:1184-8.
21. Shaw MJ, Talley NJ, Beebe TJ, et al. Initial validation of a diagnostic questionnaire for gastroesophageal reflux disease. Am J Gastroenterol 2001;96:52-7.
22. Belafsky PC, Postma GN, Koufman JA. Validity and reliability of the reflux symptom index (RSI). J Voice 2002;16:274-9.
23. Wiklund IK, Junghard O, Grace E, et al. Quality of life in reflux and dyspepsia patients. Psychometric documentation of a new disease-specific questionnaire (QOLRAD). Eur J Surg Suppl 1998;583:41-9.
24. Revicki DA, Wood M, Wiklund I, et al. Reliability and validity of the Gastrointestinal Symptom Rating Scale in patients with gastroesophageal reflux disease. Qual Life Res 1998;7:75-83.
25. Kim HJ, Kwon CI, Kessler WR, et al. Long-term follow-up results of endoscopic treatment of gastroesophageal reflux disease with the MUSE endoscopic stapling device. Surg Endosc 2016;30:3402-8.
26. Corley DA, Katz P, Wo JM, et al. Improvement of gastroesophageal reflux symptoms after radiofrequency energy: a randomized, sham-controlled trial. Gastroenterology 2003;125:668-76.
27. Coron E, Sebille V, Cadiot G, et al. Clinical trial: radiofrequency energy delivery in proton pump inhibitor-dependent gastro-oesophageal reflux disease patients. Aliment Pharmacol Ther 2008;28:1147-58.
28. Raymond JM, Marquis P, Bechade D, et al. Assessment of quality of life of patients with gastroesophageal reflux. Elaboration and validation of a specific questionnaire [French]. Gastroenterol Clin Biol 1999;23:32-9.
29. McHorney CA, Ware JE Jr, Lu JF, et al. The MOS 36-item Short-Form Health Survey (SF-36): III. Tests of data quality, scaling assumptions, and reliability across diverse patient groups. Med Care 1994;32: 40-66.
30. Aziz AM, El-Khayat HR, Sadek A, et al. A prospective randomized trial of sham, single-dose Stretta, and double-dose Stretta for the treatment of gastroesophageal reflux disease. Surg Endosc 2010;24:818-25.
31. Perry KA, Banerjee A, Melvin WS. Radiofrequency energy delivery to the lower esophageal sphincter reduces esophageal acid exposure and improves GERD symptoms: a systematic review and meta-analysis. Surg Laparosc Endosc Percutan Tech 2012;22:283-8.
32. Lipka S, Kumar A, Richter JE. No evidence for efficacy of radiofrequency ablation for treatment of gastroesophageal reflux disease: a systematic review and meta-analysis. Clin Gastroenterol Hepatol 2015;13:1058-67; e1.
33. Savary M, Miller G. The Esophagus. Handbook and Atlas of Endoscopy. Solothurn: Gassmann Verlag, AG; 1978.
34. Dughera L, Rotondano G, De Cento M, et al. Durability of Stretta radiofrequency treatment for GERD: results of an 8-year follow-up. Gastroenterol Res Pract 2014;2014:531907.
35. Noar M, Squires P, Noar E, et al. Long-term maintenance effect of radiofrequency energy delivery for refractory GERD: a decade later. Surg Endosc 2014;28:2323-33.
36. Triadafilopoulos G. Stretta: a valuable endoscopic treatment modality for gastroesophageal reflux disease. World J Gastroenterol 2014;20:7730-8.